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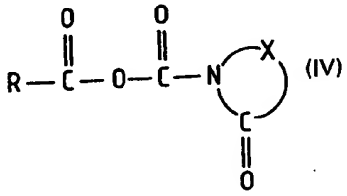
(71) Applicant
Sour Pliva farmaceutska, kemijska prehrambena i kozmeticka industrija, Ive Lole Ribara 89, 41000 Zagreb, Yugoslavia
(72) Inventors
Mice Kovacevic,
Juraj Herak,
Branimir Gaspert
(74) Agent
Pollak, Mercer & Tench, High Holborn House, 52/54 High Holborn, London WC1V 6RY

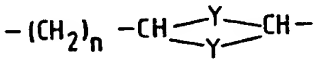
(54) Carboxylic Acid Amides

(57) Carboxylic acid amides which are sensitive compounds, including the penicillins and cephalosporins, are made by reacting a carboxylic acid with an N-chlorocarbonyl-*sec*-amide to form a mixed anhydride of the formula:

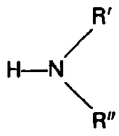


(IV)

wherein R is a C_{1-5} alkyl, cycloalkyl of up to C_8, aryl, aralkyl with up to C_5 in the alkyl moiety or heterocyclic and X is bis[mono-(C_1—C_6)alkyl], C_{1-6} alkylene, a C_{1-4} group with N, O or S as a heteroatom or

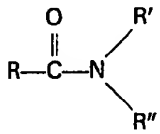


where Y is a C_{1-5} group or a C_{0-4} group with N, O or S as a heteroatom and *n* is 0—3, and subjecting the mixed anhydride to aminolysis with an amine of the formula:



(V)

wherein R′ and R″ are each H, C_{1-5} alkyl, cycloalkyl of up to C_8, aralkyl having up to C_5 in the alkyl moiety or heterocyclic. The carboxylic acid amide products have the formula:



(I)

wherein R, R′ and R″ are as defined above.

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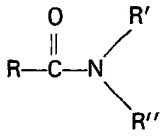
The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Carboxylic Acid Amides

This invention relates to the manufacture of carboxylic acid amides of the general formula:



(I)

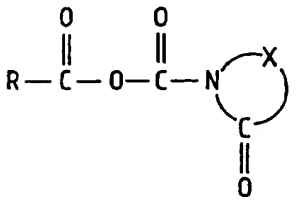
wherein R represents a C_{1-5} alkyl group, a cycloalkyl group having up to 6 carbon atoms, an aryl group, an aralkyl group having up to 5 carbon atoms in the alkyl moiety or a heterocyclic group, R′ and R″ are the same or different and each represents a hydrogen atom or a C_{1-5} alkyl group, a cycloalkyl group having up to 6 carbon atoms, an aralkyl group having up to 5 carbon atoms in the alkyl moiety or a heterocyclic group and wherein R, R′ and R″ each may be substituted or unsubstituted.

The compounds of formula I are known and are used as pharmaceuticals, since *inter alia* they comprise the penicillins and cephalosporins.

There is a known method for the manufacture of amides by selective aminolysis of mixed anhydrides, e.g. anhydrides of carboxylic acids or mono-esters of carbonic acid (A. L. J. Beckwith, The Chemistry of Amides, Publ. J. Zabicky, Intersc. Publsh., London 1970, p. 91), which is of especial importance in the preparation of amides of sensitive carboxylic acids and amines, which include functional groups which can react with conventional reactants in the preparation of carboxylic acid amides according to other preparation methods. Therefore, this known method is most frequently used in the synthesis of peptides (P. Stelzel, Methoden der organischen Chemie-Houben-Weyl, Publ. E. Wünsch, Vol XV/2, Ed. IV, G. Tieme Verlag, Stuttgart 1974, p. 171) as well as in the synthesis of semisynthetic penicillins and cephalosporins (F. P. Doyl, J. H. Nayler, Advances in Drug Research, Publ. N. J. Haper & Simmonds, Vol 1, Acad. Press, London 1964, p. 1).

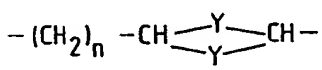
However, this method suffers from certain disadvantages owing to competing side-reactions, e.g. disproportionation and formation of the symmetrical anhydride of the starting carboxylic acid from two molecules of the mixed anhydride, thus reducing the yield of the final product, as in this case the symmetrical anhydride reacts only with one part of the amine. In some cases, it has further been ascertained that urethane results from a non-selective aminolysis of the mixed anhydride and the preferably nucleopholic reaction of the amine with the "alkoxy" carbonylic group. One reason for these side reactions is undoubtedly based on the presence of the O-alkyl group in the mixed anhydride [N. F. Albertson, Org. Reaction, Vol. *12* (1962) 179].

It has now been found that compounds of general formula I, comprising, *inter alia*, amides of sensitive carboxylic acids, may be prepared by selective aminolysis of mixed anhydrides of the general formula:

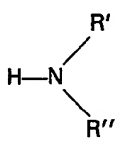


(IV)

wherein R has the meaning defined above and X is a bis-[mono-C_1—C_6-alkyl] group, a C_{1-6} alkylene group, a C_{1-4} group comprising a heteroatom selected from N, O and S or a group of the formula



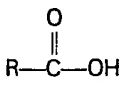
wherein Y is a C_{1-5} group or a C_{0-4} group, comprising a heteroatom selected from N, O and S and *n* is an integer from 0 to 3, with an amine of the general formula:



(V)

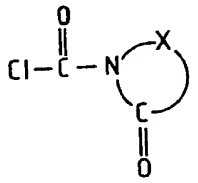
wherein R′ and R″ each have the meaning defined above.

The mixed anhydrides of general formula IV are easily obtained by the reaction of carboxylic acids of the general formula:



(II)

wherein R has the meaning defined above, with an N-chlorocarbonyl-*sec*-amide of the general formula:



(III)

wherein X has the meaning defined above.

The process of the present invention is preferably carried out in such a manner that the carboxylic acid II is dissolved in an appropriate inert organic solvent, most suitably methylene chloride or tetrahydrofuran, in the presence of an organic base, e.g. pyridine or triethylamine, at a temperature of −10° to +10°C and most preferably about 0°C, whereupon the N-chlorocarbonyl-*sec*-amide III is added. Alternatively, a solution of the carboxylic acid and the organic base can be added to the solution of N-chlorocarbonyl-*sec*-amide, prepared prior to the reaction.

The subsequent selective aminolysis of the resulting mixed anhydride IV with the amine V is preferably conducted at a temperature of −5° to +5°C, most preferably 0°C, using the same solvent as in the above preparation of the intermediate product IV.

The reaction time for preparation of the intermediate IV may typically range from 5 to 30 minutes, whereas the selective aminolysis takes about 1 hour, in either case under stirring.

The reactants may conveniently be employed in equimolar quantities, although an excess of up to 10 mol % of the carboxylic acid or the amine is feasible, depending upon the specific reactants.

The organic base and the N-chlorocarbonyl-*sec*-amide are added in equimolar quantities with respect to the carboxylic acid or in an excess of up to 5—15 mol %.

The resulting product I is isolated from the reaction mixture and purified in conventional manner, e.g. by the addition of water, separation of the organic layer and successive washing thereof with dilute HCl, water, $NaHCO_3$ solution and water, or alternatively, the solvent is removed from the reaction mixture by evaporation, whereupon water is added and it is worked up in the aforesaid manner. The resulting product is finally purified by recrystallization from a suitable solvent.

The invention is illustrated, but in no way limited, by the following Examples.

Example 1
N-Benzylamide of Phenylacetic Acid

a) Phenylacetic acid (6.8 g, 50 mmole) was dissolved in methylene chloride (100 ml), triethylamine (5.05 g, 50 mmole) was then added and the reaction solution was cooled to 0°C. A solution of N-chlorocarbonylpyrrolidin-2-one (7.35 g, 50 mmole) in methylene chloride (100 ml) was added dropwise over a period of 10 minutes and the reaction solution was stirred for a further 20 minutes at 0°C. A solution of benzylamine (5.35 g, 50 mmole) in methylene chloride (100 ml) was added dropwise over a period of 10 minutes, after which stirring was continued for 1 hour at the same temperature.

After the addition of water (200 ml), the solution was stirred for 2 minutes, whereupon the layers separated, the organic layer was washed with water (100 ml) and dried and subsequently the solvent was evaporated. The residual solid was washed with ether and dried.

Yield: 8.2 g (73%)
m.p.: 118°—120°C
lit. m.p.: 122°C (Bell. E I, *12*, 458)

b) A solution of 3-chlorocarbonyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one (554 mg, 2 mmole) in methylene chloride (10 ml) was cooled to 0°C and, over a period of 10 minutes, a solution of phenylacetic acid (272 mg, 2 mmole) in pyridine (182 mg, 2.3 mmole) and methylene chloride (6 ml) was added dropwise. The reaction mixture was stirred for 30 minutes at 0°C, whereupon a solution of benzylamine (215 mg, 2 mmole) in methylene chloride (5 ml) was added over a period of 10 minutes. Stirring of the solution was continued for a further 2 hours at 0°C, whereupon water was added (10 ml), the layers separated and the organic layer was washed with 0.1 N HCl and with water and then dried. Evaporation of the organic solvent and washing of the solid residue with ether yielded the desired product in a quantity of 340 mg (75.6%); m.p. 120°C.

Exampl 2
Benzylamid of N-benzyloxycarbonyl-D-alpha-phenylglycine

a) N-Benzyloxycarbonyl-D-alpha-phenylglycine (11.4 g, 40 mmole) was dissolved in methylene chloride (100 ml) in the presence of pyridine (3.2 g, 40 mmole) at 0°C. A solution of N-chlorocarbonyl-

pyrrolidin-2-one (6.2 g, 42 mmole) in methylene chloride (50 ml) was then added with stirring and the stirring was continued for a further 20 minutes. A solution of benzylamine (4.3 g, 40 mmole) in methylene chloride (50 ml) was added dropwise over a period of 15 minutes and the reaction mixture was then stirred for 1 hour at the same temperature. After the addition of water (150 ml), layers separated and the organic layer was washed and dried and the solvent was separated by distillation under reduced pressure. The solid residue obtained was washed with ether and dried.

Yield: 12.85 g (85.7%), m.p. 186°—190°C

IR spectrum (KBr): 3310(s), 1688(s), 1650(vs), 1520(s), 1245(s), 750(m) and 695(s) cm^{-1}

^1H NMR spectrum (DMSO-d_6) δ: 4.28 (d, J=6 Hz; N—CH_2), 5.06 (s; OCH_2), 5.34 (d, J=8 Hz; N—CH), 6.9—7.7 (m; 3 C_6H_5), 7.97 (d, J=8 Hz; OCONH), 8.75 (m; CONH)

b) A solution of 3-chlorocarbonyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one (554 mg, 2 mmole) in methylene chloride (10 ml) was cooled to 0°C, and over a period of 10 minutes, a solution of N-benzyloxycarbonyl- D-alpha-phenylglycine (570 mg, 2 mmole) in pyridine (182 mg, 2.3 mmole) and methylene chloride (6 ml) was added. Then, a solution of benzylamine (215 mg, 2 mmole) in methylene chloride (5 ml) was added over a period of 10 minutes, whereafter the stirring was continued for 1 hour at 0°C. After the addition of water, the layers separated and the organic layer was washed and dried. After evaporation of the solvent, the residual solid was washed with ether and dried.

Yield: 620 mg (82.6%), m.p. 188°—190°C

Example 3

N-Benzyloxycarbonyl-L-phenylalanyl-glycine Methylester

N-benzyloxycarbonyl-L-phenylalanine (15 g, 50 mmole) was dissolved in tetrahydrofuran (100 ml), pyridine (4 g, 51 mmole) was added and the mixture was cooled to 0°C. A solution of N-chlorocarbonyl-pyrrolidin-2-one (7.35 g, 50 mmole) in tetrahydrofuran (100 ml) was added dropwise with stirring at 0°C. The stirring was continued for 20 minutes, whereupon a solution of methyl-glycine (4.35 g, 50 mmole) in tetrahydrofuran (100 ml) was added dropwise and stirring was continued for a further 15 minutes at the same temperature. The solvent was removed by distillation under reduced pressure and the residue was dissolved in a mixture of methylene chloride and water (100:100 ml), the organic layer was separated, washed with water and dried. The resultant solid residue was recrystallized from a mixture of ethyl acetate and petroleum ether.

Yield: 13 g (70%)

m.p.: 112°—113°C

lit. m.p. 112°C [Ann. *694* (1966) 190]

Example 4

N-Benzyloxycarbonyl-D-alpha-phenylglycyl-L-phenylalanine Methylester

N-Benzyloxycarbonyl-D-alpha-phenylglycine (5.7 g, 20 mmole) was dissolved in methylene chloride (120 ml), pyridine (1.6 g, 20 mmole) was added and the mixture was cooled under stirring to 0°C. Subsequently, a solution of N-chlorocarbonyl-pyrrolidin-2-one (2.96 g, 20 mmole) in methylene chloride (50 ml) was added over a period of 10 minutes at the same temperature. After 15 minutes, a solution of L-phenylalanine methylester (3.58 g, 20 mmole) in methylene chloride (50 ml) was added over a period of 10 minutes, whereupon stirring was continued for a further 1 hour at 0°C. Subsequently, water was added, the layers separated, the organic layer was washed with water and dried. The solvent was removed by distillation and the residue was washed with ether.

Yield: 6.87 g (77%), m.p. 166°—168°C

IR spectrum (KBr): 3320(s), 1735(s), 1685(s), 1645(s), 1520(s), 1230(s) and 700(s) cm^{-1}

Example 5

Benzyl Ester of 6-[N-(benzyloxycarbonyl)-D-(—)-alphaphenyl-glycylamido]-penicillanic Acid

a) N-Benzyloxycarbonyl-D-alpha-phenylglycine (5.7 g, 20 mmole) was dissolved in methylene chloride (100 ml), cooled to 0°C, pyridine was added (1.6 g, 21 mmole), whereupon with stirring a solution of N-chlorocarbonyl-pyrrolidin-2-one (2.95 g, 20 mmole) in methylene chloride (50 ml) was added. The mixture was stirred for 30 minutes and then a solution of the benzyl ester of 6-amino-penicillanic acid (5.8 g, 19 mmole) in methylene chloride (100 ml) was added. The mixture was stirred for a further 1 hour at a temperature of 0°C, water was added, the layers separated and the organic layer was washed with water, dried and, subsequently, the solvent was removed by evaporation under reduced pressure. The product was obtained in the form of a frothy residue.

Yield: 8.7 g (80%)

IR ($CHCl_3$) and ^1H NMR ($CDCl_3$) spectra are identical to the data given in literatur (DE—OS 2 364 759).

b) A solution of 3-chlorocarbonyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one (554 mg, 2 mmole) in methylene chloride (10 ml) was cooled to 0°C, a solution of N-benzyloxycarbonyl-D-alpha-phenylglycine (670 mg, 2 mmole) in pyridine (182 mg, 2.3 mmole) and methylene chloride (5 ml) was added, whereupon the mixture was stirred for a further 5 minutes at

0°C. Then, a solution of the benzyl ester of 6-aminopenicillanic acid (406 mg, 1.4 mmole) in methylene chloride (5 ml) was added dropwise, whereupon stirring was continued for 1 hour at 0°C. Subsequently, water was added, the layers separated, the organic layer was washed with water and dried. After evaporation of the solvent, the solid residue was digested with ethyl acetate (20 ml), stirred for 15 minutes and the crystals of 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one which separated were aspirated and washed with ethyl acetate (375 mg, 87%). The ethyl acetate filtrate was washed with a saturated $NaHCO_3$ solution (10 ml) and then water (2×10 ml), dried and the solvent was removed by evaporation.

Yield: 654 mg (83%) of the product as defined in a) above.

c) A solution of N-chlorocarbonyl-enantholactam (3.8 g, 20 mmole) in tetrahydrofuran (50 ml) was added over 10 minutes, with stirring at −10°C, to a solution of N-benzyloxycarbonyl-D-alpha-phenylglycine (5.7 g, 20 mmole), triethylamine (4.2 g, 21 mmole) and tetrahydrofuran (100 ml), whereupon the mixture was stirred for a further 20 minutes. Subsequently, a solution of the benzyl ester of 6-aminopenicillanic acid (5.8 g, 19 mmole) in tetrahydrofuran (50 ml), was added, the reaction mixture was stirred for 2 hours at −10°C, whereupon the solvent was evaporated from the reaction mixture, the residue was dissolved in ethyl acetate (100 ml) and water (100 ml), the aqueous layer was separated, washed with water, a saturated $NaHCO_3$ solution and again water and finally dried. Evaporation of the solvent yielded 8.5 g (78.4%) of the product as defined in a) above.

Example 6

2,2,2-Trichloroethyl ester of 7-[N-(2,2,2-trichloroethyloxycarbonyl)-D-alpha-phenylglycylamido]-3-methyl-3-cephem-4-carboxylic Acid

a) N-2,2,2-Trichloroethyloxycarbonyl-D-alpha-phenylglycine (6.54 g, 20 mmole) was dissolved in methylene chloride (100 ml), cooled to 0°C, pyridine (1.6 g, 20 mmole) was added and subsequently a solution of N-chlorocarbonyl-pyrrolidin-2-one (2.95 g, 20 mmole) in methylene chloride (50 ml) was added dropwise over 15 minutes. The reaction mixture was stirred for 30 minutes at the same temperature, whereupon a solution of the 2,2,2-trichloroethyl ester of 7-aminodeacetoxycephalosporanic acid (5.76 g, 16.7 mmole) in methylene chloride (100 ml) was added. The reaction mixture was stirred for 1 hour at 0°C and water (150 ml) was added. The organic layer was separated and was washed with water, 5% w/w HCl, 5% w/w $NaHCO_3$ and finally again with water. After drying, the solvent was evaporated and the residue was crystallized from carbon tetrachloride.

Yield: 8.6 g (78.2%), m.p. 96°C, lit. m.p. 95°C.

IR and ^1H NMR spectra are identical to the data given in the literature [R. R. Chauvette et al, J. Org. Chem. *36* (1971) 1259].

b) A solution of 3-chlorocarbonyl-8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one (554 mg, 2 mmole) in methylene chloride (10 ml) was cooled to 0°C and a solution of N-2,2,2-trichloroethyloxycarbonyl-D-alpha-phenylglycine (654 mg, 2 mmole) in pyridine (160 mg, 2 mmole) and methylene chloride (5 ml) was added, the mixture was stirred for 5 minutes at 0°C, whereupon a solution of the 2,2,2-trichloroethyl ester of 7-aminodeacetoxycephalosporanic acid (576 mg, 1.67 mmole) in methylene chloride was added. The mixture was stirred for 1 hour at the same temperature, whereupon water was added to the solution and the product as indicated in Example 5b was isolated.

Yield: 850 mg (77.3%) of the product, showing the same characteristics as the product obtained in a) above.

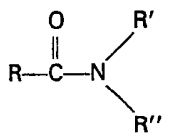
Regenerated: 355 mg (83%) of 8-acetyl-7,7-dimethyl-6-thia-3,8-diazabicyclo[3,2,1]octan-2-one.

c) A solution of N-chlorocarbonyl-N-propyl-benzamide (4.5 g, 20 mmole) in methylene chloride (100 ml) was cooled to −5°C, whereupon a solution of N-2,2,2-trichloroethyloxycarbonyl-D-alpha-phenylglycine (6.54 g, 20 mmole) in pyridine (1.6 g, 20 mmole) and methylene chloride (50 ml) was added and the mixture was stirred for 30 minutes at −5°C. A solution of the 2,2,2-trichloroethyl ester of 7-aminodeacetoxycephalosporanic acid (5.76 g, 16.7 mmole) in methylene chloride (50 ml) was added to the reaction mixture and finally it was worked up as indicated in a) above.

Yield: 8.25 g (75%) of the product, having the same characteristics as the product obtained in a) above.

Claims

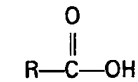
1. A process of manufacture of a carboxylic acid amide of the general formula:



(I)

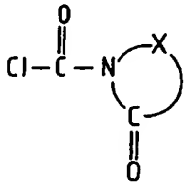
wherein R represents a C_{1-5} alkyl group, a cycloalkyl group having up to 6 carbon atoms, an aryl group, an aralkyl group having up to 5 carbon atoms in the alkyl moiety or a heterocyclic group, R′ and R″ are

the same or different and each represents a hydrogen atom or a C_{1-5} alkyl group, a cycloalkyl group having up to 6 carbon atoms, an aralkyl group having up to 5 carbon atoms in the alkyl moiety or a heterocyclic group and wherein R, R′ and R″ each may be substituted or unsubstituted, wherein a carboxylic acid of the general formula:



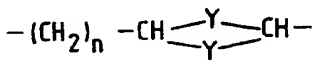
(II)

wherein R has the meaning defined above, is reacted with an N-chlorocarbonyl-*sec*-amide of the general formula:

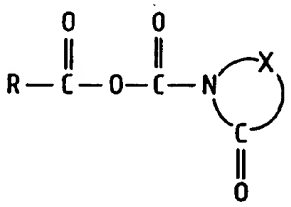


(III)

wherein X is a bis[mono-C_1—C_6-alkyl] group, a C_{1-6} alkylene group, a C_{1-4} group comprising a heteroatom selected from N, O and S or a group of the formula

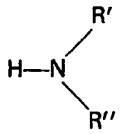


wherein Y is a C_{1-5} group or a C_{0-4} group comprising a heteroatom selected from N, O and S and *n* is an integer from 0 to 3, so as to form a mixed anhydride of the general formula:



(IV)

wherein R and X have the meanings defined above, and the resultant product IV is subjected to selective aminolysis by means of an amine of the general formula:



(V)

wherein R′ and R″ each have the meaning defined above.

2. A process as claimed in claim 1, wherein the carboxylic acid (II) is reacted with the amide (III) at a temperature in the range from −10° to +10°C in an inert organic solvent and in the presence of an organic base.

3. A process as claimed in claim 1 or 2, wherein selective aminolysis of the anhydride (IV) is carried out at a temperature within the range from −5° to 5°C.

4. A process as claimed in claims 2 and 3, wherein the selective aminolysis is carried out in the same solvent as that used in the reaction of the carboxylic acid (II) with the amide (III).

5. A process as claimed in claim 2, 3 or 4, wherein the solvent is methylene chloride or tetrahydrofuran.

6. A process as claimed in claim 2 or in claim 3, 4 or 5 as dependent thereon, wherein the organic base is pyridine or triethylamine.

7. A proc ss as claimed in claim 1, substantially as described with reference to any of the for going Examples.

8. A carboxylic acid amide of formula I, when manufactured by a process as claimed in any preceding claim.

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